http://mnj.ub.ac.id/
DOI: 10.21776/ub.mnj.2022.008.02.13
eISSN: 2442-5001 **pISSN:** 2407-6724
Accredited by DIKTI Decree No: 21/E/KPT/2018

MALANG NEUROLOGY JOURNAL MNJ

REVIEW OPEN ACCESS

BIOMARKERS AND PROGNOSTIC SCORING IN CEREBRAL MALARIA

Orlando Pikatan[1], Ellen Ferlita Tirtana[1], Kezia Seraphine[1], Wienta Diarsvitri[1], Prawesty Diah Utami[1]

Correspondence: *orlando.pikatan@gmail.com*
[1]Faculty Medicine of Hang Tuah University, Surabaya, Indonesia

Article History:
Received: August 3, 2021
Accepted: February 17, 2022
Published: July 1, 2022

Cite this as:
Pikatan O, Tirtana EF, Seraphine K, Diarsvitri W, Utami PD. Biomarkers and prognostic scoring in cerebral malaria. Malang Neurology Journal; 2022.8:140-143. DOI: http://dx.doi.org/10.21776/ub.mnj.2022.008.02.13

ABSTRACT

Malaria remains a public health concern and remain the deadliest in infectious disease in the world. Cerebral malaria is a particularly severe complication of this disease and associated with high mortality. This literature review is made up from 19 literatures consisting of journals, and book. The literature review used data base www.pubmed.com, and www.scholar.google.com using "cerebral malaria and biomarker, predictor of cerebral malaria and treatment of severe malaria". The languages for this journal are English and Indonesian. From the collection of literatures in this literature review, severe consists of cerebral malaria, blackwater fever, acute kidney injury, pulmonary edema, electrolyte disturbance, hematology disturbance, and obstetrics emergency resulting from malaria which is postpartum hemorrhage. Cerebral malaria increases the mortality of the patient, so they have to be diagnosed early and treated precisely. Patients with infection of plasmodium falciparum and GCS<11 must be suspected as cerebral malaria. Biomarker examination such as Soluble ICAM-1, Specific muscle's protein, Angiopoetin-1 and 2, and Plasma microparticles is the most precise way to detect malarial emergency earlier Coma Acidosis Malaria score is also found to be useful in predicting the prognosis in cerebral malaria. Early diagnosis should be made as early as possible to reduce mortality from malaria and its emergencies.

Keywords: Cerebral malaria, biomarkers in malaria, severe malaria.

Introduction

Malaria remains a public health concern, and remain the deadliest in infectious disease in the world. Malaria cases were reported 216 millions by 91 countries word wide in 2016. Causing 445 000 deaths each year world-wide.[1,2]

Malaria is caused by *Plasmodium* infection, although all types of *plasmodium* is dangerous, but *Plasmodium falciparum* is considered as the most dangerous. Complications from malaria are life-threatening as it may cause damage to special organs such as the brain (cerebral malaria). Cerebral malaria is a serious neurological complication caused by *Plasmodium* falciparum. Cerebral malaria can increase the mortality of *plasmodium* infected patients, increasing 20% of all adults that's is infected by *Plasmodium falciparum*.[3,4]

Methods

This literature review is made up from 19 literatures consisting of journals, and book. The literature review used data base www.pubmed.com, and www.scholar.google.com using "cerebral malaria and biomarker, predictor of cerebral malaria and treatment of severe malaria". The languages for this journal are English and Indonesian

Review

Malaria is a parasitic disease caused by *Plasmodium* infection. Severe malaria is an infectious disease with one of the disorders of renal impairment, jaundice, respiratory distress, metabolic acidosis, and cerebral malaria.[3,5] The most cerebral malaria is usually caused by P. *falciparum* and the most dangerous. There are two neuropathogenesis of cerebral malaria that are mechanical hypothesis and cytokine storm. The mechanical hypothesis is based on the ability of this parasite to induce erythrocytes undergo cytoadherence with vascular endothelium. Parasites that infect erythrocytes will express P. *falciparum* Erythrocyte Membrane Protein 1 (PfEMP1). PfEMP1 functions as ligand in cytoadherence. PfEMP1 will be expressed in knobs which assists in attachment to the endothelium. This protein also helps in avoiding immune system and differentiation from endothelial receptor binding. In cerebral blood vessels, ICAM-1 is an important receptor that binds specifically to PfEMP1, this bond will produce cytoadhesion which results in sequestration of erythrocyte cells that have been infected with parasites, resulting in hypoxia as well as microcirculation blockade. Further, impaired perfusion will be made worse by infected and non-infected erythrocyte attachment and clumping of

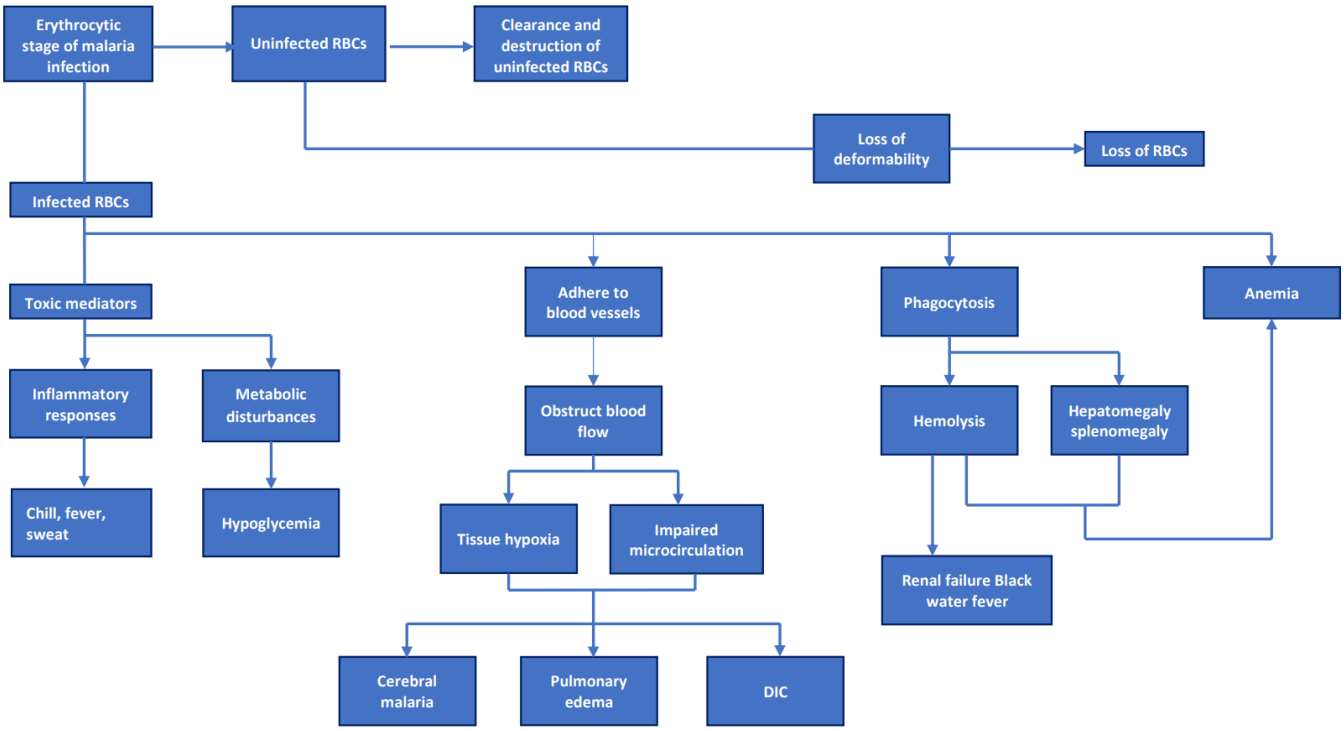

Figure. 1. Pathogenesis of Malarial.[8]

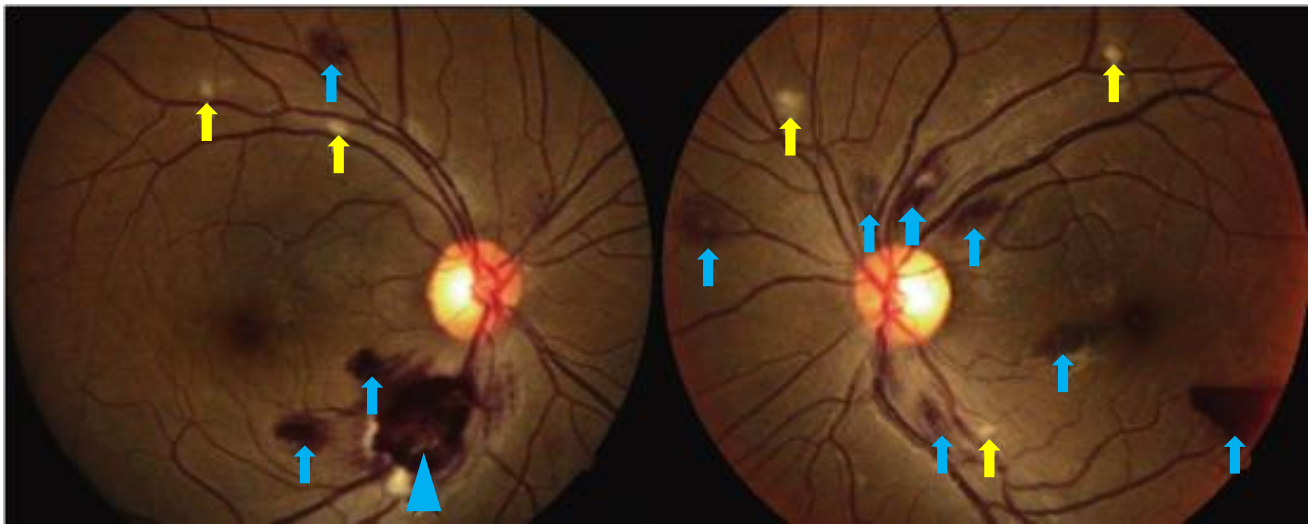

Figure 2. Malaria retinopathy with a hemorrhage (blue arrow) and retinal whitening (yellow arrow).[12]

infected erythrocyte cells. Cerebral Malaria has the most severe complication of P. falciparum infection. Cerebral malaria is a collection of neurological symptoms with patients in unarousable coma (GCS <11 in adults caused by *Plasmodium* falciparum infection.[6,7]

Symptoms of cerebral malaria are range from simple delirium into coma. The onset of coma may happen after seizure, and seizure occurs 15 % in adult and generally tonic clonic.[9,10]

Upon neurological examination, passive resistance can be found against neck flexion eye often shows a divergent gaze with normal oculocephalic reflex. In direct ophthalmoscope, retinal bleeding is found in 15% of patients, but the bleeding is rarely related to the macula. This bleeding is shaped like a ship or fire. White appearance in the retina and cotton wool spot can also be seen.[8]

The diagnosis of cerebral malaria requires definitive evidence of malaria infection, the discovery of the asexual form of *Plasmodium falciparum* in peripheral blood smear of patients with fever with unarousable coma and GCS <11 in adults. Seizure is often found in malaria (general seizure is more frequent than focal). Seizure may due to the infection of *plasmodium* or the antimalarial itself such as mefloquine.[11]

Fundal examination in patients with cerebral malaria shows retinal abnormalities in 40% of patients. Malaria retinopathy consists of retinal whitening (macula or peripheral), discoloration of blood vessels (white or orange), retinal bleeding, and papilledema. The previous two are typical of severe *falciparum* malaria.[11]

Forced jaw closure and tooth snapping (bruxism) are common in cerebral malaria. Neurological findings are usually symmetrical. Motor abnormalities such as

Table 1. Biomarker[18]

Biomarker	Examination Method	Result
Soluble ICam-1 (sICAM-1)	Plasma examination with ELISA	Increasing of sICAM-1 shows the cerebral malaria
Plasma micropatricles (MP)	Blood specimen with biochemistry examination	MP mediates coagulation, inflammation and adhesion process that facilitates neurological lesion
VWF	Plasma specimen with Elisa	Indicates high and acute endothelial activation. [21]
Angiopoetin	Blood specimen with Elisa	ANG-1 and ANG-2 blood concentration are the accurate marker to differentiate complicate and uncomplicated malaria
Pf Histidine-rich protein-2 (PfHRP2)	Cerebro Spinal fluid with Elisa examination	PfHRP2 elevation indicates the distinction of severe malaria and uncomplicated malaria

Table 2. CAM Score [19]

	Score		
Variable	**0**	**1**	**2**
Base deficit	<2	2 to <10	≥10
GCS	15	>10 to 14	≤10
Bicarbonate score	≥24	15 to <24	<15
Respiratory rate score	<20	20 to <40	≥40

The CAM score ≥ 2 is an indicator of mortality and morbidity.[20]

decerebrate rigidity, decorticate rigidity or opisthotonos can be found. Muscle tone and tendon reflexes increase.[4]

Imaging can be used to exclude other possibilities. Ct-scan and MRI showed a nonspecific finding such as brain edema, or infarct in sub cortical areas. Brain edema is the consequence of an increase in cerebral blood volume due to the sequestered erythrocyte.[10,13]

Laboratory test is important in Malaria cerebral diagnosis. Confirmation by the discovery of the *plasmodium* is really important. [13] Thick and thin smear with Giemsa stain are important to do. Some situations such as the patient is taking the antimalarial drug or sequestration of infected red blood cell can lead to false negative and examination must be repeated again every 12 hours up to 48 hours. Other test such as Rapid Manual Test (RMT) to detect antigen or Polymerase Chain Reaction (PCR) to detect Specific *plasmodium* DNA can be used for *plasmodium* detection.[13,14]

Blood electrolyte examination can be a useful in cerebral malaria prognostic predictor. Hyponatremia is a common disorder that's found in severe malaria, and Parida *et al.*, reported that Hyponatremia is associated with high mortality in severe malaria.[15]

Lactate serum, is also useful on predicting the mortality of cerebral malaria, on Chaudhari *et al.*, serum lactate was examined and high of lactate serum (>45 mg/dl) lead to high chance mortality (54% of all patients with increasing lactate died).[16]

Biomarkers are often used for a lot of diseases to predict the disease. In cerebral malaria, currently lack of reliable markers for predicting the mortality and the prognostic of this disease. Currently, there are only candidate for this marker. The markers are *Plasmodium falciparum* histidine-rich protein 2, intra-cellular adhesion molecule-1 (ICAM-1), Von Willebrand factor (VWF), and angiopoetin.[17]

ICAM-1 play an important role in sequestration of *Plasmodium falciparum*-infected red blood cell (PRBC). Binding ICAM-1 to PRBC show the development of cerebral malaria. Thus, high levels of plasma soluble ICAM-1 is associated with the development of cerebral malaria. Angiopoetin-1 and -2 (ANG-1 and -2) are also reliable biomarkers for cerebral malaria. They regulate endothelial activation and integrity. ANG-1 and -2 serum or whole blood levels can be used to discriminate cerebral, severe non-cerebral, and uncomplicated malaria. Cerebral malaria patients present significant decrease in ANG-1 and increase in ANG-2 levels and the ratio of ANG-2:ANG-1. *Plasmodium falciparum* histidine rich protein 2 (PfHRP2) may be used to confirm the presence of parasite in severe malaria patients and to distinguish severe and uncomplicated malaria.[18]

Other than biomarker, Scoring can be used to determine the prognosis of severe malaria. CAM (Coma Acidosis Malaria score is a scoring system that contains base deficits, GCS, bicarbonate score, and respiratory rate score. [19]

Conclusion

Cerebral malaria remains the most dangerous of all complication in malaria. To establish the diagnosis, evidence of plasmodium infection must be found along with the clinical condition of the patient, fever with unarousable coma and GCS <11 in adults or Blantyre coma scale <3 in children.

Early diagnosis must be made if we encounter patient with this disease. Symptoms such as loss of consciousness, seizures and bruxism should lead us to consider the diagnosis of cerebral malaria. Early biomarkers test might be promising for clinician to diagnosis cerebral malaria precisely. However, it's hard to use biomarkers as a routine test nowadays because not much experiments about the biomarkers have been conducted and the capability in testing them is limited. So, experiments about the biomarkers must be done more in the future.

Acknowledgement

None.

Conflict of Interest

There is no conflict of interest in this review article.

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